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Facts About **Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)**

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a highly aggressive, historically difficult-to-diagnose hematologic malignancy with a poor prognosis. In recent years, better understanding of the biology of BPDCN has led to improved diagnosis. Additionally, the US Food and Drug Administration (FDA) recently approved the targeted therapy tagraxofusp-erzs (ELZONRIS™) for the treatment of BPDCN. This approval, improved diagnosis, and additional therapies currently in development have the potential to improve outcomes moving forward. This publication will explain the history, diagnosis, and current treatment practices for BPDCN, detail the efficacy and safety data for tagraxofusp-erzs, and review several investigational therapies currently in clinical trials.

Highlights

- BPDCN has an estimated incidence of 1,000 to 1,400 annually in the US and Europe combined.
- While BPDCN can occur at any age, the median age at diagnosis is in the mid-60s, with approximately 75% of cases occurring in men.
- Historically, initial response to combination chemotherapy has been high, but patients regularly relapse with a median overall survival of approximately 1 year. These regimens are often associated with significant side effects and poor tolerability.
- 80%–90% of patients with BPDCN present with skin lesions. Early recognition can lead to timely diagnosis and management.
- Accurate diagnosis requires a biopsy showing the morphology of plasmacytoid dendritic blast cells and immunophenotypic criteria established by either immunohistochemistry or flow cytometry.
- Immunohistochemical criteria for BPDCN include positivity for CD123, CD4, CD56 and TCL1 in the absence of myeloperoxidase and lysozyme.
- While never evaluated in a prospective trial, historically, patients who have received high-dose acute leukemia-based chemotherapy followed by an allogeneic stem cell transplant during the first remission appeared to have the best outcomes.
- Tagraxofusp-erzs (SL-401; ELZONRIS™) is approved for the treatment of BPDCN in adults and children 2 years of age and older. Tagraxofusp-erzs is a targeted therapy directed to CD123 (IL-3R), a cell surface receptor highly expressed in BPDCN.
- Additional therapies are currently under investigation for the treatment of BPDCN.

Background and Prevalence

BPDCN is a highly aggressive malignancy derived from the precursors of plasmacytoid dendritic cells (pDCs), immune cells that specialize in the production of type I interferons in response to bacterial and viral stimuli.[1-3] Accurate diagnosis of this malignancy has been complicated by a number of factors, including shifting nomenclature over the years – BPDCN has been referred to as agranular CD4+ natural killer cell leukemia, blastic natural killer-cell leukemia/lymphoma and CD4+/CD56+ hematodermic neoplasm.[1,4-6] As understanding of the biology and origin of this malignancy has improved, the World Health Organization (WHO) established the term *blastic plasmacytoid dendritic cell neoplasm* (BPDCN) in 2008.[6] BPDCN is currently classified by the WHO as a distinct entity within the myeloid neoplasm and acute leukemia classification.[7]

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Background and Prevalence, cont.

It is difficult to precisely estimate the incidence of BPDCN due to its rarity, evolving terminology and likely underdiagnosis, but it is thought to represent an estimated 1,000 to 1,400 cases annually in the US and Europe combined.[1] BPDCN is typically a disease of the middle-aged and elderly, with a median age at diagnosis in the mid- 60s.[1,2,8,9] Approximately 3 times as many males as females are affected.[1,2,8] Pediatric cases have also been described in children as young as 8 months of age.[10,11] Historically, patients diagnosed with BPDCN have a poor prognosis with a median overall survival (OS) from diagnosis of approximately 1 year despite the use of combination chemotherapy.[1,3,4,12-14]

Presentation

Early recognition of BPDCN has been challenging, because its clinical features can be heterogeneous and can overlap other hematologic malignancies.[3,4,15,16] There can be a significant delay between the onset of symptoms and diagnosis.[17] Improved understanding of the biology of BPDCN in recent years and increased awareness by clinicians and pathologists will likely lead to improved diagnostic timelines.

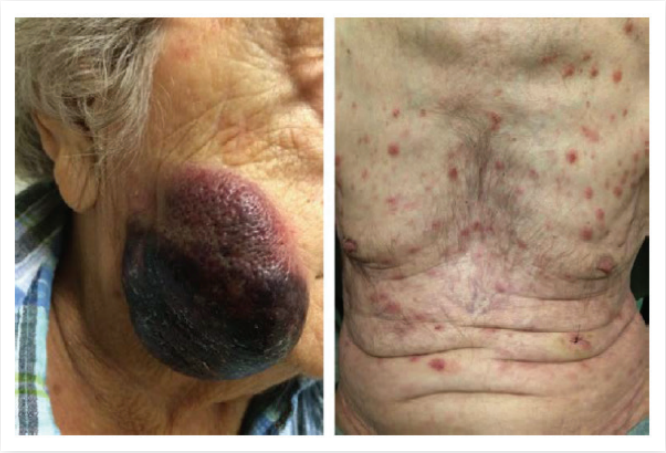
Cutaneous

Approximately 80%-90% of patients diagnosed with BPDCN present with skin lesions. These lesions may appear to be indolent initially, but progression invariably occurs with involvement of multiple sites including bone marrow, peripheral blood, lymph nodes, liver, spleen and, in some cases, the central nervous system (CNS).[2,4,9,13,16]

Cutaneous lesions vary in size, shape, color and distribution and can be confused with other benign and malignant skin lesions **(Figure 1)**.[1,17,18] They can appear as bruise-like or erythematous papules, plaques or tumors measuring up to 10 cm, commonly on the face, trunk and extremities, although they can occur anywhere.[1,17,18] BPDCN is often detected incidentally by dermatologists, and differentiating BPDCN from other lesions is critically important. When BPDCN is suspected, consultation with a dermatopathologist or hematopathologist is advised and assessment for the immunohistochemical criteria for BPDCN is recommended (see below).[1,13]

A significant percentage (40% to 50%) of patients initially present with involvement of the bone marrow and lymph nodes.[8,18] Extracutaneous involvement that may be observed at presentation includes lymph nodes, spleen, liver, tonsils, and the CNS.[16,18]

Figure 1. Cutaneous lesions in BPDCN



Courtesy of Shapiro R, et al. J Cell Sci Ther. 2015;S8. doi:10.4172/2157-7013.S8-008.[8]

Leukemic

In over half of cases, BPDCN patients present with skin lesions and bone marrow involvement characteristic of acute leukemia.[19] In fewer cases, BPDCN patients may present with bone marrow disease without skin involvement.[1,4,13,17,19] In most of these cases cytopenia is also present, with highly variable rates of bone marrow infiltration.[19] BPDCN may co-exist with or have a preceding malignancy such as myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) in approximately 10% to 20% of cases,[20] and thus hematologic malignancies with BPDCN markers and/or skin lesions should be screened for the presence of BPDCN.[1,8,18]

Diagnosis

Many patients with BPDCN present with what may appear to be indolent disease, but due to the invariable progression and extremely poor prognosis, rapid and accurate diagnosis is critical for planning appropriate therapy. Identification of several pDC-related antigens in recent years has aided this effort.[17] Diagnosis of BPDCN requires a biopsy showing the morphology of plasmacytoid dendritic blast cells and immunophenotypic criteria established by either immunohistochemistry or flow cytometry, depending on what tissue is available for analysis.[1] Most cases of BPDCN are diagnosed with a skin biopsy.[17]

The immunohistochemical criteria for BPDCN include positivity for CD123, CD4, CD56 and TCL-1 in the absence of other myeloid leukemia markers, particularly myeloperoxidase and lysozyme. CD56 can be negative in rare cases, which does not rule out BPDCN if the other markers are positive.

Other pDC-associated markers, such as CD2AP or CD303/BDCA2 may also be used to confirm the diagnosis.[1-3,8,15,17,19] Markers that can be used to distinguish BPDCN from acute myeloid leukemia (AML), leukemia cutis (LC), and myeloid sarcoma (MS) are shown in **Table 1**.[1] Atypical immunophenotypes have been reported, however, in which common markers such as CD4 and CD56 are absent.[4,17] Myeloid markers, including CD33, CD68 and CD43, may also be expressed in BPDCN.[1,3,4,13]

Table 1. Immunohistochemical markers for BPDCN[1]

		BPDCN	AML/LC/MS
SHARED MARKERS	CD4	80%-100%	10%-20%
	CD56	90%-100%	5%-50%
	CD123	85%-100%	15%-45%
	TCL1	80%-100%	5%-20%
UNIQUE MARKERS		CD2AP	MPO
		CD303/BDCA-2	Lysozyme
			CD34
			CD14
			CD11c
			CD163

Range of positive cases are shown for shared markers. AML = acute myeloid leukemia; LC = leukemia cutis; MS = myeloid sarcoma; CD = "cluster of differentiation"; TCL1 = T-cell leukemia 1; CD2AP = CD2-associated protein; BDCA-2 = blood dendritic cell antigen 2; MPO = myeloperoxidase.

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If BPDCN presents as the leukemic form or if there is bone marrow involvement, flow cytometry is appropriate. A recent study has demonstrated that BPDCN can be successfully distinguished from AML, T-cell lymphoblastic leukemia/lymphoma, and NK-cell lymphoma/leukemia using a 10-color AML flow cytometry panel.[3]

Treatment

Prior to the approval of tagraxofusp-erzs in December 2018, there were no approved therapies for the treatment of BPDCN. Additionally, due to the lack of prospective clinical trials there had been no universally accepted standard of care.[1,2,4,9] The tagraxofusp-erzs clinical trial that led to its approval was the first prospective multicenter trial in BPDCN.

Historically, induction therapy with non-Hodgkin lymphoma (NHL)-, acute lymphoblastic leukemia (ALL)-, or acute myeloid leukemia (AML)-type chemotherapy regimens had resulted in high initial response rates (complete response [CR] = 40% to 90%).[1,3] While never compared prospectively, patients given ALL-like regimens appear to do better.[2,3,19] Relapse occurs frequently with any of these regimens (50% to 90%), with a median OS of approximately 1 year.[1,3,4,13,14] Today, tagrazofusp-erzs should be considered in all eligible patients diagnosed with BPDCN.

Stem cell transplantation (SCT) should be considered when patients have achieved a complete remission and are sufficiently fit. Long-term remissions have been seen with allo-SCT done during the first remission.[1,2] Relapse following transplantation occurs in approximately 30% of patients.[1] Transplantation beyond the first remission or in patients who have not achieved a complete remission appears to have a negative effect on OS and progression-free survival.[1,2] While auto-SCT has been used for consolidation and can improve survival, allo-SCT during the first remission has appeared to offer the best results.[1,2]

A recent study has shown CNS involvement in the majority of BPDCN cases at presentation (60%) despite patients having no neurologic symptoms.[21] The CNS is also a potential site of relapse.[1,4] Systemic or intrathecal chemotherapy for CNS prophylaxis during treatment has been recommended for BPDCN patients in some guidelines, although prospective data supporting this approach is lacking.[2,3,21]

BPDCN is generally a disease of people in their 60s and older, and fitness for aggressive systemic chemotherapy and conditioning for transplant have been recognized as challenges in this population. The approval of tagraxofusp-erzs and several additional therapies currently in clinical trials are welcome developments.

Therapies Targeting CD123

CD123 (interleukin-3 receptor alpha subunit, or IL-3Rα) is highly expressed in BPDCN (in addition to a wide range of other hematologic malignancies) and minimally expressed on normal cells, suggesting it is an appropriate target for therapy.[1,2] There is currently 1 approved therapy for BPDCN that targets CD123, and 3 additional such therapies under investigation.

Tagraxofusp-erzs (SL-401)

Tagraxofusp-erzs (SL-401, ELZONRIS™) is a recombinant fusion protein consisting of human IL-3 (the natural ligand of CD123) fused to a truncated diphtheria toxin (DT) engineered such that IL-3 replaces the native DT receptor binding domain.[2,22-24] The IL-3 domain of SL-401 directs the cytotoxic DT payload to cells expressing CD123. Upon internalization, tagraxofusp-erzs inhibits protein synthesis and induces apoptosis of the target cell.

Tagraxofusp-erzs received FDA approval in December 2018 for the treatment of BPDCN in adults and children 2 years of age and older.[25]

In 29 first-line patients who received the optimal dose of tagraxofusp-erzs in the pivotal trial (12 mcg/kg/day), the overall response rate was 90%, with a 72% rate of complete response (CR) plus complete response with minimal residual skin abnormality (CRc). Of these patients, 45% were successfully bridged to SCT.[26]

In 15 patients with relapsed or refractory disease, 1 patient achieved a CR and 1 patient achieved a CRc (duration 111 and 424 days, respectively), for a CR/CRc rate of 13.3%.[26]

Among 94 patients with newly-diagnosed or relapsed/refractory myeloid malignancies, including 58 patients with BPDCN, who received tagraxofusp-erzs at the recommended dose and schedule, the most common adverse reactions (≥ 30%) were capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia and weight increase. The most common laboratory abnormalities (incidence ≥ 50%) were decreases in albumin, platelets, hemoglobin, calcium, sodium, and increases in glucose, ALT and AST.[25]

Investigational Therapies

CD123CAR with Truncated Epidermal Growth Factor Receptor

Chimeric antigen receptor (CAR) T- cell therapy leverages the natural ability of the human immune system to attack and destroy cancer cells. CARs are genetically engineered cell surface receptors that equip T cells with the abilities to recognize and bind antigens found on tumor cells and activate the T cell to kill the target cell. (More information about CAR T-cell therapy can be found here: *Facts About CAR T-Cell Therapy*.)

A phase 1 study with CD123-directed CAR T-cells is underway in patients with AML and BPDCN. In addition to the CD123-binding domain, this CAR construct includes a truncated epidermal growth factor receptor (EGFRt). The EGFR sequence lacks the EGF binding domain and intracellular signaling domain but retains the epitope for the anti-EGFR monoclonal antibody cetuximab. This provides a traceable marker for the CAR T cells and a potential mechanism to destroy them – a CAR T-cell "off switch" – in the event of life-threatening toxicities, which could provide a desirable safety measure for this emerging therapy.[27]

A phase 1 dose-finding and safety study is ongoing in relapsed/refractory AML and persistent or recurrent BPDCN. (ClinicalTrials.gov Identifier: NCT02159495)

XmAb14045

XmAb14045 is a bispecific antibody that binds two targets, CD123 and CD3. It functions to "bring together" tumor cells expressing CD123 and cytotoxic T cells, which bind CD3. The T cells are then activated to kill the CD123-expressing target cells.

A phase 1 study to determine the safety and tolerability of XmAb14045 is currently underway in patients with CD123-expressing hematologic malignancies, including AML, B-cell ALL, BPDCN, and chronic myeloid leukemia (CML). In February 2019, the FDA placed the phase 1 trial on partial clinical hold following two patient deaths.[28] (ClinicalTrials.gov Identifier NCT02730312)

IMGN632

IMGN632 is an antibody-drug conjugate that consists of a humanized anti-CD123 antibody fused to an indolino-benzodiazepine agent (IGN). When delivered to a target cell via the anti-CD123 antibody, the IGN payload alkylates DNA without crosslinking, which kills the CD123-expressing target cell.[29]

A phase 1 trial in patients with CD123-expressing hematologic malignancies including ALL, BPDCN, myeloproliferative neoplasms and AML is ongoing. (ClinicalTrials.gov Identifier NCT03386513)

Additional Targets

Nivolumab (Opdivo®)

Nivolumab is an antibody that blocks programmed death receptor-1 (PD-1). PD-1 serves as an immune system "checkpoint," preventing the immune system from destroying normal cells displaying its ligands PD-L1 and PD-L2. Studies have shown that tumor cells often express PD-L1, allowing them to evade the immune response. Nivolumab can prevent PD-L1 from binding to PD-1, "unleashing" the immune system to destroy the cancer cells. Nivolumab is approved to treat multiple malignancies, including metastatic melanoma, renal cell carcinoma, and non-small cell lung cancer.

A phase 2 study is currently underway to determine how patients with relapsed and refractory peripheral T-cell lymphomas or BPDCN respond to nivolumab. (ClinicalTrials.gov Identifier NCT03075553)

Venetoclax

Venetoclax (Venclexta®) is an orally bioavailable small molecule that inhibits the anti-apoptotic protein BCL-2. Venetoclax is FDA-approved for treatment of patients with chronic lymphocytic leukemia (CLL), and, in combination with chemotherapy, in a subset of patients with acute myeloid leukemia (AML). Venetoclax is currently being tested alone and as part of combination therapy in many hematologic malignancies. A recent study found that BPDCN cells are highly dependent on BCL-2 for survival and are sensitive to treatment with venetoclax. In that study, 2 patients were treated off-label with venetoclax and experienced significant clinical benefits.[30] A formal clinical trial of venetoclax in BPDCN is underway. (ClinicalTrials.gov Identifier: NCT03485547)

Conclusion

BPDCN is a hematologic malignancy with a highly aggressive clinical course and a historically poor prognosis. The recent FDA-approval of tagraxofusp-erzs (SL-401) is an exciting development for eligible patients, offering an alternative to aggressive chemotherapy. This approved therapy, in addition to numerous targeted therapies in clinical trials, has the potential to improve outcomes.

It is recommended that all treated patients that achieve remission be considered for allogeneic SCT.

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